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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	Gras-Masse, et al.	Examiner:	M.F. Salvoza
Serial No.:	09/555,780	Group Art Unit:	1648
Filed:	November 17, 2000	Docket:	1091-2 PCT/US/RCE
Confirmation No:	9478	Dated:	December 9, 2005
For:	MIXED LIPOPEPTIDE MICELLES FOR INDUCING AN IMMUNE RESPONSE AND THEIR THERAPEUTIC USES		

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APPEAL BRIEF PURSUANT TO 37 C.F.R. §41.37

Sir:

This is an appeal to the Board of Appeals from the examiner's final rejection of the claims dated April 7, 2005. A timely Notice of Appeal was filed on October 7, 2005, and received by the United States Patent and Trademark Office on October 11, 2005. This Brief is being filed in triplicate under the provisions of 37 C.F.R. §1.192.

I. REAL PARTY IN INTEREST

The real parties in interest are:

1) Institut National de la Sante et de la Recherche Medicale (INSERM), 101 Rue de Tolbiac, 75654 Paris Cedex 13, France, an assignee herein.

2) Centre National de la Recherche Scientifique, 3 Rue Michel Ange, 75794 Paris Cedex 16, France, an assignee herein.

3) Institut Pasteur de Lille, 1 Rue du Professeur Calmette, Boite Postale 245, 59019 Lille Cedex, France, an assignee herein.

II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are know to Appellants or Appellants' legal

representative which will directly affect, or be directly affected by, or have a bearing on, the Board's decision on this appeal.

III. STATUS OF CLAIMS

The status of the claims in this application is:

A. Total Number of Claims in Application

Claims in the application are: Claims 1-25.

B. Status of all the Claims

1. Claims cancelled: None.
2. Claims withdrawn from consideration but not cancelled: Claims 8, 12-14, 16, 20 and 25.
3. Claims pending: Claims 1-18
4. Claims allowed: None.
5. Claims rejected: Claims 1-7, 9-11, 15, 17-19, 21-24.
6. Claims objected to: Claims 5 and 22.

C. Claims on Appeal

The claims on appeal are: Claims 1-7, 9-11, 15, 17-19, 21-24.

IV. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the final rejection of the claims dated April 7, 2005.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Claim 1 is repeated below.

> A composition for inducing an immune response, comprising micelles or micro-aggregates wherein each micelle or micro-aggregate comprises:

more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, and
a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit.

The claims comprise the following elements, each of which is followed by a reference to the specification by page and line number.

Element 1: composition for inducing an immune response (page 4, line 18; page 4, lines 24-26)

Element 2: micelles or micro-aggregates (page 4, line 17)

Element 3: wherein each micelle or micro-aggregate comprises: more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit (page 6, lines 3-14)

Element 4: wherein each micelle or micro-aggregate comprises: a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit (page 6, lines 11-12)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claim Rejection - 35 U.S.C. §103

Claims 1-7, 9-10, 15, 17-19 and 21-24 were rejected over Stuhler et al. (*Proc. Natl. Acad. Sci.*, 1997, 94:622-627), Sastry et al. (*AIDS*, 1991, 5:699-707), and Sugimoto et al. (*J. Immunol.* 1978, 120:980-982, abstract only). According to the examiner:

> Sastry teaches eliciting cell-mediated immunity with micelles comprising short HIV envelope peptides of gp160 with two palmitic residues attached in acetic acid. Therefore, Sastry does teach a composition comprising more than one lipopeptide.

> Although they are derived from a single gp160 protein from HIV, the peptides derived from it contain more than one CTL determinant. One of ordinary skill in the art would have had a reasonable expectation to prepare lipid micelle polymers containing either a mixture of peptides or at least more than one peptide. In addition, if anything, Sastry teaches the importance of the selection of each peptides, but does not necessarily preclude the use of more than one. Furthermore, one of ordinary skill in the art at the time the invention was made would have been motivated to present various portions of a protein in the form of peptides, as Sastry et al. do, to ensure that the immune system is uniformly presented with a complete set of epitopes from the antigenic peptide.

Claim 11 was rejected over Stuhler et al., Sastry et al., and Sugimoto et al. and further in view of Kramer et al. According to the examiner:

> ... claim 11, which is dependent on independent claim 1, is rejected for the same reasons that claim 1 is unpatentable in further view of Kramer.

Claim 18 was rejected over Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al., and further in view of Shapiro et al. According to the examiner:

> ... since a combination of the cited references lead to the claimed composition, the addition of the teachings of Shapiro et al. meet the limitations of claim 18 drawn to a method according to claim 17 wherein the dispersing of the lipopeptides dissolved in acetic acid is confirmed by a two-dimensional nuclear magnetic resonance method.

Claim Objections

Claim 5 was objected to due to informalities. According to the examiner:

> it is grammatically incorrect, since the claim needs the preposition "to" to complete the prepositional phrase "according to."

Claim 22 was objected to due to informalities. According to the examiner:

> it is grammatically incorrect, since the claim uses the language "wherein the at least one lipid unit."

Claim Rejection - 35 U.S.C. §112

Claim 24 was rejected for allegedly being indefinite. According to the examiner:

> claim 24 depends improperly on canceled claim 20.

VII. ARGUMENT

Background and General Description of Invention

Antigens are substances that are foreign to a host, and recognized by the host's immune system. Examples of antigens include viruses and bacteria. The host's immune response recognizes a portion of an antigen, known as an epitope. The epitope constitutes the antigenic determinant.

In order to stimulate the immune system, an antigenic determinant must be presented to specialized immune cells. Antigenic determinants are presented to such immune cells by antigen presenting cells (APC). An APC typically presents an antigenic determinant to two types of immune cells, (i) T helper lymphocytes (HTL) and (ii) cytotoxic T lymphocytes (CTL).

Antigenic determinants that are recognized by receptors on T helper lymphocytes are called HTL antigenic determinants. Conversely, antigenic determinants that are recognized by receptors on cyotoxic T lymphocytes are called CTL antigenic determinants.

It was known at the time of the present invention that there are two types of immune

responses. The first type of immune response is referred to as a humoral immune response. The humoral response is characterized by production of antibodies.

The second type of immune response is referred to as a cytotoxic immune response. The cytotoxic immune response is mediated by cytotoxic T lymphocytes.

For the benefit of the board, appellants present a somewhat simplified schematic of the basic concepts necessary to understand the arguments made in the appeal in figure 1, which is attached as exhibit A. Figure 1 shows the steps that occur during an immune response.

As shown in step 1 of figure 1, the first step in an immune response is the association of an antigenic determinant to an APC. The association of the antigenic determinant to an APC results in formation of an APC/antigenic determinant complex.

In the case of a humoral immune response, the APC is a B cell, and the antigenic determinant is an HTL antigenic determinant. Therefore, the complex formed in a humoral immune response will be referred to as a B cell/HTL antigenic determinant complex.

For a cytotoxic immune response, the APC is usually not a B cell, and the antigenic determinant is a CTL antigenic determinant. Therefore, the complex formed in a cytotoxic immune response will be referred to as an APC/CTL antigenic determinant complex.

As shown in step II of figure 1, the APC/antigenic determinant complex presents the bound antigenic determinant to a T lymphocyte. The T lymphocyte binds to the APC/antigenic determinant complex to form an APC/antigenic determinant/T lymphocyte complex.

There are two kinds of T lymphocytes relevant to the present discussion. In a humoral immune response, the T lymphocyte is a T helper lymphocyte. In a cytotoxic immune

response, the T lymphocyte is a cytotoxic T lymphocyte.

Consequently, in a humoral immune response, the APC/antigenic determinant/T lymphocyte complex is a B cell/HTL antigenic determinant/T helper lymphocyte complex. In a cytotoxic immune response, the APC/antigenic determinant/T lymphocyte complex is an APC/CTL antigenic determinant/cytotoxic T lymphocyte complex.

As shown in step III of figure 1, proteins, called cytokines, are secreted from T helper lymphocytes. The cytokines activate the cells in the APC/antigenic determinant/T lymphocyte complex. In a humoral response, the activated cell is a B cell. In a cytotoxic immune response, the activated cell is a cytotoxic T lymphocyte. The activated cells produce the immune response.

When B cells become activated, they produce antibodies. When T cytotoxic lymphocytes becomes activated, they mediate the cytotoxic immune response, e.g., by attacking virus infected cells.

To summarize, activation of B cells and production of antibodies in a humoral immune response requires T helper lymphocytes and HTL antigenic determinants. Activation of cytotoxic T lymphocytes in a cytotoxic immune response requires cytotoxic T lymphocytes and CTL antigenic determinants.

One of the references cited by the examiner, *Stuhler et al.*, reported that induction of a cytotoxic immune response in an organism requires both CTL and HTL antigenic determinants to be present on the surface of the same APC. See figure 2 attached as exhibit B. Under such circumstances, the CTL antigenic determinant can be recognized by cytotoxic T lymphocytes at the same time that the HTL antigenic determinant is recognized by T helper lymphocytes.

Thus, the value of delivering both CTL antigenic determinants and HTL antigenic determinants to an APC, *in vitro*, was recognized in the prior art. However, *Stuhler et al.* does not teach how to make a composition to achieve an immune response *in vivo* (i.e., vaccine). In particular, *Stuhler et al.* does not disclose a composition for delivering two types of antigenic determinants to the same APC *in vivo*.

The invention relates to a composition useful for rectifying this deficiency of the prior art. The composition comprises micelles or micro-aggregates containing antigenic determinants.

A micelle is a globule of molecules. The molecules generally have non-polar groups on one end of the molecule, and polar groups on the other end of the molecule. An example of a non-polar group is a lipid. An example of a polar group is a peptide. In water, the molecules are arranged so that the non-polar groups face inward, while the polar groups face outward such that the polar groups are in contact with the water molecules. A micro-aggregate is a less organized small cluster of molecules.

Each micelle or micro-aggregate contains more than one first lipopeptide and a second lipopeptide. Each first lipopeptide comprises at least one CTL antigenic determinant and at least one lipid unit. The second lipopeptide comprises at least one HTL antigenic determinant and at least one lipid unit. Therefore, the composition of the claimed invention contains a mixture of more than one first lipopeptide containing at least one CTL antigenic determinant, and a second lipopeptide containing at least one HTL antigenic determinant. (These elements will be referred to below as "the claimed elements.")

Rebuttal of Rejection under 35 U.S.C. §103

As mentioned above in section (VI) ("Grounds of Rejection to be Reviewed on Appeal"), various combinations of claims 1-7, 9-11, 15, 17-19, 21-24 were rejected under 35

U.S.C. §103 over a number of references.

Rejection of claims 1-7, 9-10, 15, 17-19, and 21-24 under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al.*, and *Sugimoto et al.*

On page 3 of the final Office Action, Examiner Salvoza rejected all of the pending claims (1-7, 9-10, 15, 17-19, and 21-24) under 35 U.S.C. §103(a) as being obvious over three references: *Stuhler et al., Sastry et al.*, and *Sugimoto et al.*

Reason 1 why the claimed invention is not obvious over the combination of Stuhler et al., Sastry et al. and Sugimoto et al.: Sastry et al. teaches away from the claimed invention.

The purpose of the experiments conducted by Sastry et al. is to obtain a cytotoxic immune response "**without ... antibody production**." See line 1 of the abstract. As a first step towards this purpose, Sastry et al. identified **potential** T lymphocyte antigenic determinants **without B cell activity**. See first full paragraph on page 703 of Sastry et al.

It is well known to those skilled in the art that antibodies are produced by activated B cells. It is also well known to those skilled in the art that the activation of B cells require HTL antigenic determinants. See attached figure 1.

Therefore, *Sastry et al.* teaches against the use of HTL antigenic determinants.

One requirement of the claimed composition is the presence of at least one HTL antigenic determinant. Since *Sastry et al.* **teaches away** from HTL antigenic determinants, *Sastry et al.* teaches away from the invention.

In re Fine, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988), is an authoritative decision of the Federal Circuit in which a reference "warns against rather than teaches" a claimed invention. The court held that it is "error to find obviousness where references diverge from and teach away from the invention at hand." Therefore, since *Sastry et al.* teaches away from the

presently claimed invention, it is error to find obviousness in the disclosure of *Sastry et al.*

Accordingly, maintenance of the rejection of claims 1-7, 9-10, 15, 17-19 and 21-24 under 35 U.S.C. §103(a) over *Sastry et al.* is clearly untenable.

Reason 2 why the claimed invention is not obvious over the combination of Stuhler et al., Sastry et al. and Sugimoto et al.: Lack of suggestion or motivation to combine Stuhler et al. and Sastry et al.

In order to maintain a proper obviousness rejection over a combination of references, there must be motivation to combine the references. *In re Fine,* ("...teachings of references can be combined *only* if there is some suggestion or incentive to do so (original emphasis)"). *In re Lee*, 277 F.3d 1338, 1343-44 (Fed. Cir. 2002) ("The factual inquiry whether to combine references must be thorough and searching... It must be based on objective evidence of record.")

As appellants demonstrate below, the examiner has not provided the requisite motivation to combine *Stuhler et al* and *Sastry et al.*

Stuhler et al. shows that the induction of a good cytotoxic immune response involves the presentation of **both** CTL and HTL antigenic determinants. See second full paragraph on page 624. As stated above and depicted in figure 1, it was known at the time of the present invention that HTL antigenic determinants induce an immune response involving the production of antibodies. Therefore, *Stuhler et al.* suggests that a good cytotoxic immune response **requires the production of antibodies**.

The contrast between *Stuhler et al.* and *Sastry et al.* is abundantly clear. The authors of *Sastry et al.* wished to obtain a good CTL immune response "**without ... antibody production**." See above.

Thus, Stuhler et al. require production of antibodies for a good CTL response. In stark

contrast, Sastry et al. want to prevent the production of antibodies.

Due to the divergent teachings of Stuhler et al. and Sastry et al., one skilled in the art would have been dissuaded from combining the disclosures of *Stuhler et al.* and *Sastry et al.* Thus, there is more than simply a lack of motivation for one skilled in the art to combine the *Stuhler et al.* and *Sastry et al.* references in the manner suggested by the examiner.

As stated above, *Sastry et al.* actually teaches away from the disclosure of *Stuhler et al.*, and from the claimed invention. Therefore, it would be illogical for a person having ordinary skill in the art to combine *Sastry et al.* and *Stuhler et al.*

Accordingly, maintenance of the rejection of claims 1-7, 9-10, 15, 17-19 and 21-24 under U.S.C. §103(a) over *Sastry et al.* and *Stuhler et al.* is clearly untenable.

Reason 3 why the claimed invention is not obvious over the combination of Stuhler et al., Sastry et al. and Sugimoto et al.: Sugimoto et al. is not material to patentability.

In the examiner's previous Office Action dated July 5, 2001, the examiner states that *Stuhler et al.* uses keyhole limpet hemocyannin as a T helper antigenic determinant. The examiner conceded that *Stuhler et al.* does not disclose or suggest hemagglutinin as a T helper antigenic determinant.

In order to rectify this deficiency of *Stuhler et al.*, the examiner cites *Sugimoto et al.* According to the examiner, *Sugimoto et al.* discloses that hemagglutinin elicits a similar immune response as that elicited by keyhole limpet hemocyanin. Therefore, the examiner contends that keyhole limpet hemocyanin, as disclosed in *Stuhler et al.*, can be substituted with hemagglutinin, as taught in *Sugimoto et al.* See page 5 of the July 5, 2001 Office Action.

Sugimoto et al. was cited against claim 1. Appellants still do not understand why *Sugimoto et al.* is relevant to the obviousness rejection of claim 1, which is not limited to a

particular T helper antigenic determinant.

Claim 9, which is dependent on claim 1, recites hemagglutinin. Perhaps the examiner intended to cite *Sugimoto et al.* against claim 9. Even so, claim 9 is patentable at least for the same reasons claim 1 is patentable.

Moreover, *Sugimoto et al.* does not disclose or suggest the use of micelles or micro-aggregates containing lipopeptides for generating an immune response. Therefore, *Sugimoto et al.*, either alone or in combination with *Stuhler et al.* and *Sastry et al.*, does not preclude patentability of the present claims.

Therefore, maintenance of the rejection of claims 1-7, 9-10, 15, 17-19 and 21-24 under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al.* and *Sugimoto et a*l. is clearly untenable.

Reason 4 why the claimed invention is not obvious over the combination of the Stuhler et al., Sastry et al. and Sugimoto et al.: Combination of Stuhler et al., Sastry et al and Sugimoto et al. does not teach or suggest all the claim elements.

Another criteria that must be satisfied in order to maintain a proper obviousness rejection over a combination of references is that the combination of prior art references must teach or suggest all the claim elements. *In re Royka,* 180 USPQ 580 (CCPA 1974). ("All words in a claim must be considered in judging the patentability of that claim against the prior art.")

The cited references do not disclose or suggest a composition as presently claimed. In particular, the prior art references fail to disclose a composition comprising:

(i) a first lipopeptide comprising at least one CTL antigenic determinant;

(ii) more than one first lipopeptide; and

(iii) a second lipopeptide comprising at least one HTL antigenic determinant.

The examiner conceded that "the plurality of peptides is certainly essential to applicant's invention." See page 4 of the office action dated April 7, 2005. However, the examiner asserts that "one of ordinary skill in the art would not assume from Sastry that the use of the micelles would be limited to one lipopeptide."

The examiner then states that "Sastry teaches eliciting cell-mediated immunity with micelles comprising short HIV envelope ***peptides*** of gp160 with two palmitic residues attached in acetic acid. ... Although they are derived from a single gp160 protein from HIV, the peptides derived from it contain more than one CTL determinant." Therefore, the examiner concludes that *Sastry et al.* teaches a composition comprising more than one lipopeptide.

The examiner is incorrect to conclude that one of ordinary skill would not assume from *Sastry et al.* that the use of micelles would be limited to one lipopeptide. Quite the contrary.

It is well established that a prior art reference must be considered as a whole. There are various statements in *Sastry et al.* that would lead a person having ordinary skill in the art to the conclusion that *Sastry et al.* does not disclose compositions containing more than one candidate peptide sequence.

For example, *Sastry et al.* discloses various tables and figures. Each table and figure shows a separate result for each peptide sequence. See tables 1 and 2, and figures 1 and 2. Therefore, a person having ordinary skill in the art would understand that the experiments carried out by Sastry et al. necessarily involved the *in vivo* administration of a composition containing multiple copies of **a single peptide sequence**.

In addition, the "Peptide Polymers" section on page 700 of *Sastry et al.* states the following:

> ... Two types of polymers were prepared:... (2) lipid micelle polymers formed by attaching an amino-terminal lysine to **the peptide sequence in question** and then coupling a fatty acid to both

> the alpha and epsilon amino groups ... *(Emphasis Added)*

The emphasized words "peptide sequence in question" suggest that the micelles contain one peptide sequence, and not a mixture of polymers comprising different peptide sequences, as asserted by the examiner.

Further, the "Measurement of Antibody Response" and "T-cell Proliferation Assay" sections on page 700 of *Sastry et al.* disclose that groups of three to five mice were primed with "100 μg synthetic **peptide**." Once again, the word "peptide" is stated in the singular. Thus, *Sastry et al.* discloses that each mouse was administered a composition containing one particular peptide sequence.

This deficiency of *Sastry et al.* is further supported in the first full paragraph on page 702, which states the following:

> Synthetic peptides selected from the three functionally important regions described above were tested in both the disulfide polymeric (peptides 61, 63, 65 and 67) and palmitic acid micellar (peptides 62, 64, 66, and 68) forms. ... **Each** of these peptides in the micellar form also induced anti-peptide antibodies at levels similar to respective disulfide forms. (*Emphasis Added*)

Again, the phrase "each (i.e., each one) of these peptides in the micellar form" indicates only one unique peptide sequence in the micellar form.

For all the above reasons, a person having ordinary skill in the art would clearly not perceive that the micelles of *Sastry et al.*, considered as a whole, contain more than one first lipopeptide and a second lipopeptide. Therefore, *Sastry et al.* does not disclose or suggest micelle compositions as presently claimed.

The deficiency of *Sastry et al.* is not rectified by the teachings of *Stuhler et al.* and *Sugimoto et al.* These references also do not disclose or suggest the claimed element of a composition containing more than one first lipopeptide and a second lipopeptide.

Therefore, the combination of *Stuhler et al., Sastry et al.*, and *Sugimoto et al.* does not teach or suggest all the claim elements. Accordingly, the rejection of claims 1-7, 9-10, 15, 17-19, and 21-24 under 35 U.S.C. §103 over these references is untenable for this second reason.

Rejection of claim 11 under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al., Sugimoto et al.* and further in view of *Kramer et al*.

On page 3 of the final Office Action, claim 11 was rejected under 35 U.S.C. §103(a) as being unpatentable over *Stuhler et al., Sastry et al., Sugimoto et al.* and further in view of *Kramer et al.* The examiner points to the *Kramer et al.* reference for the disclosure of the GAG 253 peptides as immunogenic sequences, and of their use in detection assays and pharmaceutical compositions.

Appellants note that claim 11 is dependent on independent claim 1. MPEP 2143.03 states: "If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is non-obvious. *In re Fine,* 5 USPQ2d 1596 (Fed. Cir. 1988)."

Appellants have provided arguments to refute the rejection of claim 1 over *Stuhler et al., Sastry et al.*, and *Sugimoto et al.* (see above). Accordingly, claim 11 is patentable at least for the same reasons that claim 1 is patentable.

Therefore, the rejection of claim 11 under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al., Sugimoto et al.* and further in view of *Kramer et al.* is clearly untenable.

Rejection of claim 18 was rejected under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al.* and further in view of *Shapiro et al.*

On page 3 of the final Office Action, claim 18 was rejected under 35 U.S.C. §103(a) as being unpatentable over *Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al.* and further in view of *Shapiro et al.* The examiner cites the *Shapiro et al.* reference for teaching the use

of two-dimensional magnetic resonance to aid in analyzing the conformation of micelle/peptide-receptor interactions.

Claim 18 is dependent on claim 17. Claim 17 is an independent claim directed to a method for producing the micelles or micro-aggregates of independent claim 1.

As discussed at length above, claim 1 is novel and non-obvious. A process of making a non-obvious product is itself unobvious. *In re Ochiai,* 71 F.3d, 1565, 37 USPQ2d 1127 (Fed. Cir. 1995). *In re Brouwer,* F.3d, 37 USPQ2d 1663 (Fed. Cir. 1996). Therefore, claim 17 is patentable at least for the same reasons that claim 1 is patentable. Claim 18 is patentable for the same reasons that claim 17 is patentable.

Accordingly, the rejection of claim 18 under 35 U.S.C. §103(a) over *Stuhler et al., Sastry et al., Sugimoto et al., Kramer et al.* and further in view of *Shapiro et al.* is clearly untenable.

Claim Objections and Rejection under 35 U.S.C. §112

In section VI above, it was noted that the examiner objected to claims 5 and 22, and rejected claim 24 under 35 U.S.C. §112, due to minor informalities. The informalities relate to grammatical issues and incorrect dependencies. All of these informalities can be easily addressed.

Appellants' representative (the undersigned) conducted a personal invention at the United States Patent and Trademark Office with Examiner Salvoza and his supervisor, Examiner Foley, on August 18, 2005. During the interview, Examiner Foley suggested that appellants' proceed directly to appeal.

Appellants informed their representative that they considered an appeal to be the most

efficient way the address the rejections of the claims. Therefore, appellants agreed with the examiner's suggestion to appeal the rejection of the claims.

The principle issues involved in the appeal are the art rejections. Appellants propose to address the minor informalities in the claims in an amendment after allowance in the event this appeal is successful.

VIII. CLAIMS APPENDIX

The claims involved in the Appeal are:

1. A composition for inducing an immune response, comprising micelles or micro-aggregates wherein each micelle or micro-aggregate comprises:

more than one first lipopeptide comprising at least one CTL antigenic determinant and at least one lipid unit, and

a second lipopeptide comprising at least one helper T antigenic determinant and at least one lipid unit.

2. A composition according to claim 1 wherein the first and second lipopeptides each comprise one or more C_4-C_{18} lipid units.

3. A composition according to Claim 1 wherein the first and second lipopeptides each comprise one or two C_4-C_{18} lipid chains linked by a covalent bond to one or two amino acids of the respective lipopeptide.

4. A composition according to Claim 1 wherein the lipid units of the lipopeptides each comprise two palmitic acid chains linked to a lysine through an NH_2 group of said lysine.

5. A composition according Claim 1 wherein the lipid units of each lipopeptide

comprises one or more of: a residue of palmitic acid, 2-aminohexadecanoic acid, oleic acid, linoleic acid, linolenic acid, pimelautide, trimexautide, or a derivative of cholesterol.

6. A composition according to Claim 1 wherein the non-lipid part of the each of the first and second lipopeptides comprises between 10 and 100 amino acids.

7. A composition according to Claim 1 wherein the helper T antigenic determinant is a multivalent antigenic determinant.

8. A composition according to Claim 1, wherein the helper T antigenic determinant is the peptide 830-843 of the tetanus toxin with the following sequence: QYIKANSKFIGITE (SEQ ID NO: 1).

9. A composition according to Claim 1 wherein the helper T antigenic determinant comprises the antigenic determinant of hemagglutinin or the PADRE antigenic determinant.

10. A composition according to Claim 1 wherein the lipopeptides comprise at least one CTL antigenic determinant selected from the group consisting of a specific protein of melanoma, a protein from HIV, a protein from HBV, a protein from papillomavirus, protein p53 and a specific protein of *Plasmodium falciparum*.

11. A composition according to Claim 1 wherein said micelles or micro-aggregates comprise one or more of the following lipopeptides:

GAG 17 EKIRLRPGGKKKYKLKHIVK(Pam)-NH_2 (SEQ ID No: 31)

GAG 253 NPPIPVGEIYKRWIILGLNKIVRMYSPTSILDK(Pam)-NH_2 (SEQ ID No: 6)

POL 325 AIFQSSMTKILEPFRKQNPDIVIYQYMDDLYK(Pam)-NH_2 (SEQ ID No: 32)

NEF 66 VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGLK(Pam)- NH_2 (SEQ ID No: 2)

NEF 116 HTQGYFPDWQNYTPGPGVRYPLTFGWLYKLK(Pam)-NH_2 (SEQ ID No:

33)

TT Ac-QYIKANSKFIGITELKKK(Pam)-NH_2 (SEQ ID No: 30).

15. A pharmaceutical composition comprising a pharmacologically effective dose of micelles or micro-aggregates according to Claim 1 and a pharmaceutically compatible vehicle.

17. A method for producing micelles or micro-aggregates according to Claim 1, comprising the following steps:

- dispersing each of the constituent lipopeptides in a solution of concentrated acetic acid of about 80% concentration then
- mixing the solutions thus obtained.

18. A method according to Claim 17 wherein the dispersing of the lipopeptides dissolved in acetic acid is confirmed by a two-dimensional nuclear magnetic resonance method.

19. A method for inducing an immune response against a particular antigen in an individual comprising administering micelles or micro-aggregates according to Claim 1 to the individual.

21. A method according to Claim 19, wherein the pathogenic agent is HIV, HBV, papillomavirus, melanoma or *plasmodium falciparum*, and wherein the antigen is an antigen of one of said pathogenic agents, or p53.

22. A composition according to Claim 1, wherein the at least one lipid unit in the second lipopeptide is different from any lipid unit in the first lipopeptide.

23. A composition according to Claim 6, wherein the non-lipid part of the

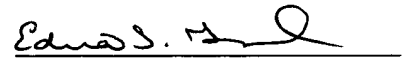
lipopeptides, comprising the antigenic determinants, comprises between 10 and 50 amino acids.

24. A method according to Claim 20, wherein the pathogenic agent is HIV, HBV, papillomavirus, melanoma, or *Plasmodium falciparum*, and wherein the antigen is an antigen of one of said pathogenic agents, or p53.

Appellant respectfully requests reversal of the rejections contained in the Office Action of April 7, 2005 for the reasons stated above.

A check in the amount of $500.00 is enclosed herewith in accordance with 37 C.F.R. §41.20(b)(2). If any additional fees are due or an overpayment has been made, please charge, or credit, our Deposit Account No. 08-2461 for such sum.

Respectfully submitted,



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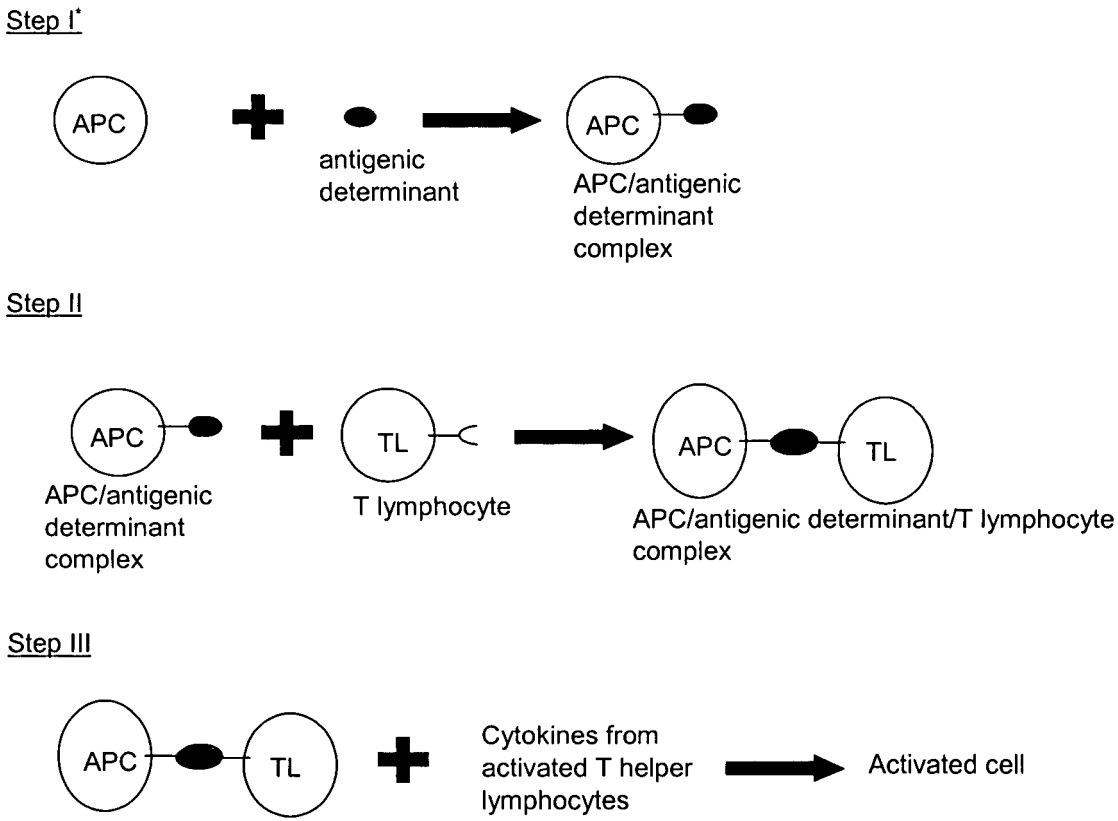

Figure 1. Schematic of immune response.

* Typically an antigenic determinant is part of a protein that is too large to be accommodated by an MHC receptor of an APC. The APC internalizes the antigen and processes the antigen into fragments (i.e., antigenic determinants) of appropriate size. The antigenic determinant then associates with an MHC receptor within the APC. The antigenic determinant/MHC complex then moves to the membrane of the APC for presentation to T lymphocytes.

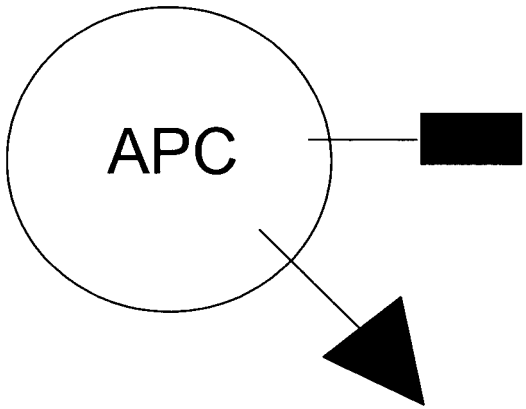

Figure 2. Schematic of APC containing both CTL and HTL antigenic determinants. ■ represents an CTL antigenic determinant; ▲represents an HTL antigenic determinant.